UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/560,268	06/14/2006	Jurgen Kleinschmidt	03528.0149.PCUS00	3309

27194 7590 10/30/2007

HOWREY LLP
C/O IP DOCKETING DEPARTMENT
2941 FAIRVIEW PARK DRIVE, SUITE 200
FALLS CHURCH, VA 22042-2924

EXAMINER
LONG, SCOTT

ART UNIT	PAPER NUMBER
1633	

MAIL DATE	DELIVERY MODE
10/30/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/560,268	KLEINSCHMIDT ET AL.	
	Examiner	Art Unit	
	Scott D. Long	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 August 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10* is/are pending in the application.

4a) Of the above claim(s) *1-8* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9 and 10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 December 2005* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The examiner of record has changed. Please direct all further correspondence to Scott Long whose phone number is 571-272-9048.

Election/Restrictions

Examiner acknowledges the election, without traverse, of Group II (claims 9-10) directed to a method of gene therapy in non-hepatic tissue, in the reply filed on 21 August 2007. The applicant further elects the species of mutant adenovirus, R484E. However, the examiner notes that neither claim 9 or 10 recites a limitation, related to the species election. Furthermore, the vector (of claim 1) used in claim 9, also does not recite the elected species.

Claim Status

Claims 1-10 are pending. However, claims 1-8 are withdrawn from further consideration by the Examiner, pursuant to 37 CFR 1.142(b), as being drawn to non-elected inventions, there being no allowable generic or linking claim. Claims 9-10 are under current examination.

Sequence Compliance

Sequence Listing and CRF have been received and are acknowledged by examiner. A statement that the Computer Readable Form (CRF) and the Sequence Listing are identical has been submitted and is acknowledged by examiner.

Oath/Declaration

The new oath or declaration, having the signatures of all inventors, received on 26 June 2006 is in compliance with 37 CFR 1.63.

Information Disclosure Statement

There are no Information Disclosure Statements (IDS) on file at the time that examination began. Therefore, examiner has not considered any Information Disclosure Statements.

Priority

This application claims benefit as a 371 of PCT/EP04/006222 (filed 6/9/2004). The application also claims benefit from foreign application EPO 03013169.2 (filed 6/11/2003). The instant application has been granted the benefit date, 9 June 2006, from the application PCT/EP04/006222.

Sequence Compliance

The disclosure is objected to because of the following:

The specification contains sequence disclosures (Figure 1) that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.82(a)(1) and (a)(2) but are not present in the Sequence Listing and/or identified in the specification by sequence identifier numbers. Applicant must provide sequence identifiers, in the case that these sequence identifier numbers. Applicant must provide sequence identifiers, in the case that these sequences are not included in the original sequence submission, a paper copy and a computer readable copy of the sequence Listing and a statement that the content of the paper and computer readable copies are the same and were applicable, include no new matter, as required by 37 CFR 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d). A full response to this Office Action must include complete response to the requirement for a Sequence Listing. The detailed description of Figure 1, should be amended to include the proper SEQ ID NO for the sequence depicted in Figure 1.

Appropriate correction is required.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 9-10 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper

definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 9-10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 9-10 require the vector of claim 1. However, the vector of claim 1 comprises at least one mutation resulting in a heparin-binding motif of a capsid protein being located within aa positions 470 to 592 showing a reduced or eliminated heparin binding function. However, the structure of the vector of claim 1 is indefinite. Which capsid protein, VP1, VP2, VP3, or other is being claimed? From which serotype of AAV vector is the capsid protein mutated? Which mutations are exactly claimed? Clarification is requested.

Claims 9-10 provide for the use of an AAV vector of claim 1, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 9-10 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The methodology for determining adequacy of Written Description to convey that applicant was in possession of the claimed invention includes determining whether the application describes an actual reduction to practice, determining whether the invention is complete as evidenced by drawings or determining whether the invention has been set forth in terms of distinguishing identifying characteristics as evidenced by other descriptions of the invention that are sufficiently detailed to show that applicant was in possession of the claimed invention (*Guidelines for Examination of Patent Applications under 35 USC § 112, p 1 "Written Description" Requirement;* (Federal Register/Vol 66. No. 4, Friday, January 5, 2001; II Methodology for Determining Adequacy of Written Description (3.)).

Claims 9-10 are broadly drawn, such that they apply to a method of gene therapy which uses a genus of adeno-associated viruses (defined by claim 1) comprising at least one mutation resulting in a heparin-binding motif of a capsid protein being located within aa positions 470 to 592 showing a reduced or eliminated heparin binding function. However, the methods employed in the working examples provided in the instant application only demonstrate individual species of adeno-associated virus, specifically heparin binding mutant #17 (R484E/R585E) in example 6 (pages 21-22). A number of other studies were performed to ascertain the importance of mutating several amino acids in the capsid protein of AAV-2 , however, no other species of AAV other than mutant #17 were tested in a method of gene delivery. In addition, all of the amino acid substitutions encompassed by the breadth of the claims is based on VP1 protein of AAC03780.1, accession number AF043303 (page 4, line 11). The specification, further states, "recombinant AAV-2 mutated in R484 and R585 showed a highly reduced infection of liver compared to wt rAAV but continued to infect heart tissue." (page 4, end of first paragraph). It seems that the scope of the genus is quite large, but the working examples are limited.

The Revised Interim Guideline for Examination of Patent Applications under 35 USC § 112, p1 "Written Description" Requirement (Federal Register/ Vol 66. No 4, Friday January 5, 2001) states "THE CLAIMED INVENTION AS A WHOLE MAY NOT BE ADEQUATELY DESCRIBED IF THE CLAIMS REQUIRE AN ESSENTIAL OR CRITICAL ELEMENT WHICH IS NOT ADEQUATELY DESCRIBED IN THE SPECIFICATION AND WHICH IS NOT CONVENTIONAL IN THE ART" (column 3, page 71434), "WHEN THERE IS SUBSTANTIAL VARIATION WITHIN THE GENUS,

ONE MUST DESCRIBE A SUFFICIENT VARIETY OF SPECIES TO REFLECT THE VARIATION WITHIN THE GENUS", "IN AN UNPREDICTABLE ART, ADEQUATE WRITTEN DESCRIPTION OF A GENUS WHICH EMBRACES WIDELY VARIANT SPECIES CANNOT BE ACHIEVED BY DISCLOSING ONLY ONE SPECIES WITHIN THE GENUS" (column 2, page 71436, emphasis added).

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "APPLICANT MUST CONVEY WITH REASONABLE CLARITY TO THOSE SKILLED IN THE ART THAT, AS OF THE FILING DATE SOUGHT, HE OR SHE WAS IN POSSESSION OF THE INVENTION. THE INVENTION IS, FOR PURPOSES OF THE 'WRITTEN DESCRIPTION' INQUIRY, *WHATEVER IS NOW CLAIMED.*" (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize the [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Considering the methods comprise a potentially large number of mutant AAV encompassed by these claims, the disclosure is not sufficient to show that a skilled artisan would recognize that the applicant was in possession of the claimed invention (genus) commensurate to its scope at the time the application was filed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 9-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bartlett et al. (US Patent 6,962,815, issued 8 November 2005) in view of Kaplitt et al. (US Patent, 6,162,796, issued 19 December 2000).

Claim 9 is directed to use of an AAV vector of claim 1 for gene therapy of a non-hepatic tissue.

Claim 10 is directed to the use according to claim 9, wherein said non-hepatic tissue is heart muscle tissue.

Because claim 9 recites the vector of claim 1, it is important to quote the limitations of claim 1 as "an AAV vector characterized in that it carries at least one mutation resulting in a heparin-binding motif of a capsid protein being located with aa positions 470 to 592 showing a reduced or eliminated heparin binding function."

Bartlett et al. teach, "Recent research on AAV has therefore involved attempts to modify the viral genome. As the range of cells that AAV will infect is so broad, some researches have focused on modifying the virus so that it targets specific types of cells for infection. The cellular range or tropism of the virus is determined by the binding of AAV capsid protein(s) to receptor and/or coreceptor proteins expressed on the surface of target cells. Heparin-sulfate proteoglycans (HSPG) is the primary cellular attachment receptor for AAV2." (col.2, lines 11-19). Bartlett et al. further teach, "AAV vectors of the invention that exhibit an altered cellular tropism may differ from wild type in that the natural tropism of AAV may be reduced or abolished" (col.4, lines 41-65). The instant application states, "Mutational analysis of AAV-2 capsid proteins VP1, VP2 and VP3, respectively showed that a group of basic amino acids (arginines 484, 487, 585, 588 and lysine 532; numbering according to the numbering based on VP1 protein id AAC03780.1 NCBI accession No. AF043303) contributes to heparin and HeLa cell binding. These amino acids are positioned in three clusters on the threefold spikes of the AAV-2 capsid." (page 4, 1st parag.). Bartlett et al. further teach amino acids 584 and 588 of VP1 as being important to heparin binding (col.17, lines 1-7 and col.41, line 26). This AAV vector contains at least one mutation to the capsid proteins in amino acid

positions 470 to 592, which affects heparin binding. Therefore, the examiner believes that Bartlett et al. teach the limitations of claim 1.

Bartlett et al. teach the limitations of claim 9, "The AAV-RGD vectors A588-RGD4C-eGFP and A588-RGD4CGLS were tested for their ability to target gene transfer to the ovarian cell lines as described in Example 9...were able to more efficiently direct gene transfer...compared to wild type AAV vector containing unmodified capsid" (col.19, lines 56-64).

Bartlett et al. do not teach specific delivery of AAV to heart muscle tissue.

Kaplitt et al. teach, "AAV naturally infects heart muscle...AAV vectors can yield long-term expression not observed with other systems" (parag.0025) and "the present invention results in gene transfer and expression to a wide area of heart muscle" (parag.0027).

Kaplitt et al. do not teach the specific mutations of capsid proteins and its corresponding effect on heparin-sulfate binding proteins as taught by Bartlett et al.

It would have been obvious to one skilled in the art to use an AAV vector having at least one mutation to the capsid proteins in amino acid positions 470 to 592, which affects heparin binding in a method of gene therapy to heart muscle tissue.

Regarding the rationale for combining prior art elements according to known methods to yield predictable results, all of the claimed elements were known in the prior art and one skilled in the art could have combined the element as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention.

Each of the elements (mutations to AAV-2 VP1 capsid protein at position 588 and AAV having a specificity for heart muscle tissue) are taught by Bartlett and Kaplitt. Bartlett, in particular, teaches that mutations of capsid proteins are capable of limiting the range of cellular targeting by AAV.

Therefore the methods as taught by Bartlett et al. in view of Kaplitt et al. would have been *prima facie* obvious over the method of the instant application.

Conclusion

No claims are allowed.

Examiner Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Scott Long** whose telephone number is **571-272-9048**. The examiner can normally be reached on Monday - Friday, 9am - 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph Woitach** can be reached on **571-272-0739**. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Scott Long
Patent Examiner
Art Unit 1633

/Janet L. Epps-Ford/
Primary Examiner
Art Unit 1633

JLE